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Alcohol and Breast Cancer

Where Are We Now and Where Do We Go from Here?

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The alcohol–breast cancer hypothesis is important because (1) breast cancer is a major source of morbidity and mortality, (2) alcohol consumption is common, and (3) drinking is modifiable. Reports from more than 50 epidemiologic investigations of this hypothesis have now appeared. A recent metaanalysis of these studies indicates both a modest positive association between alcohol and breast cancer (an approximate 25% increase in risk with daily intake of the equivalent of two drinks) and a dose–response relation. Data suggest that risk increases with consumption of alcohol in general, regardless of beverage type. Several factors, including age, weight, and estrogen usage, have been shown to modify this relation in some studies. The authors discuss a series of methodologic issues in the study of alcohol and breast cancer. These include error in alcohol assessment, difficulties in evaluating small relative risks, and the potential for confounding. Several biologic mechanisms could account for an alcohol–breast cancer relation, with increasing attention being paid to a possible mediating effect of reproductive steroid hormones. Animal studies are a relatively recent development in this area; results have been mixed. Incorporation of more refined temporal, quantitative, and qualitative indicators of alcohol exposure in future epidemiologic studies would be valuable, as would further exploration of the endocrine and other metabolic effects of moderate alcohol consumption. The alcohol–breast cancer hypothesis remains intriguing, but causality has not been established. *Cancer* 1994; 74:1101–10.

Key words: ethanol, breast neoplasms, epidemiology, metaanalysis, estrogens.

Evidence mounts that even moderate alcohol consumption increases a woman's risk of developing breast cancer. Although most research on this question has been epidemiologic, relevant findings from human metabolic and animal studies are emerging. In the current paper, we reviewed the epidemiologic literature as well as recent human metabolic and animal findings in the context of formulating a strategy for further research on the alcohol–breast cancer hypothesis.

Importance of the Alcohol–Breast Cancer Hypothesis

The possibility that alcohol consumption enhances breast carcinogenesis is important for at least three reasons.

Breast Cancer Remains a Major Source of Morbidity and Mortality Among Women

In this country, breast cancer will be diagnosed in an estimated 182,000 women and caused an estimated 46,000 deaths among women in 1993.[1] There has been a long term increase in the incidence of this disease in the United States, from 82.4 per 100,000 in 1973 to 104.6 per 100,000 in 1989.[2] Some of this increase is attributable to early detection by mammographic screening,[3] but some remains unexplained.

Alcohol Consumption Is a Common Exposure

In the Health Interview Survey conducted by the National Center for Health Statistics, 60.7% of women 18 years of age reported being "current drinkers" (consuming at least 12 drinks per year).[4] Among women who described themselves as current drinkers, 39.4% were considered light (up to three drinks per week); 27.4%, moderate (4–13 drinks per week); and 9.1%, heavy drinkers (14 or more drinks per week).

Alcohol Consumption Is Modifiable

Investigators have identified over the last several decades a number of breast cancer risk factors.[5] Many of

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these risk factors, though, are not easily amenable to modification. Alcohol consumption, however, is modifiable. If alcohol intake were causally related to the development of breast cancer, then altering of drinking patterns could make at least some dent in the morbidity and mortality stemming from this disease.

History of the Alcohol–Breast Cancer Hypothesis

An association between alcohol consumption and breast cancer was first reported in a large case–control study by Williams and Horm.[6] The study comprised approximately 600 patients with breast cancer; control subjects were patients with other cancers thought not to be related to alcohol intake. The authors reported smoking-adjusted relative risks of 1.55 and 1.28 for women consuming, respectively, 51 or more or less than 51 ounce-years (defined as the number of ounces of ethanol consumed per week multiplied by years of consumption). This investigation was hypothesis-generating in that it examined multiple potential risk factors for several cancers.

Rosenberg and colleagues reopened the alcohol–breast cancer question when they observed an alcohol–breast cancer link in a large case–control study carried out as part of a drug surveillance program in the United States.[7] These investigators studied 1152 patients with breast cancer and 519 control subjects with ovarian and endometrial cancer and 2702 nonmalignant control subjects. Among women drinking alcohol four or more times per week, compared with nondrinkers, the breast cancer relative risk was 2.0 (malignant control subjects) and 2.5 (nonmalignant control subjects); for women drinking less than four times per week, the respective relative risks were 1.5 and 1.9.

Since these findings were reported, many epidemiologic investigations of the alcohol–breast cancer hypothesis have been conducted. Reports from more than 50 studies of alcohol and breast cancer have appeared.[6–59] These studies, both case–control and cohort, have had a variety of design features and have been carried out within diverse populations in multiple countries.

For a study-by-study look at the epidemiology of alcohol and breast cancer, we refer the reader to several reviews.[60–64] We confined the current discussion to findings from an ongoing metaanalysis of epidemiologic studies of the alcohol–breast cancer association, research on factors that may modify the relation between alcohol and breast cancer, general methodologic issues in the epidemiologic approach to this question, and relevant data regarding possible mechanisms.

Metaanalysis

Longenecker and colleagues[63,64] periodically updated a metaanalysis of case–control and cohort studies of the

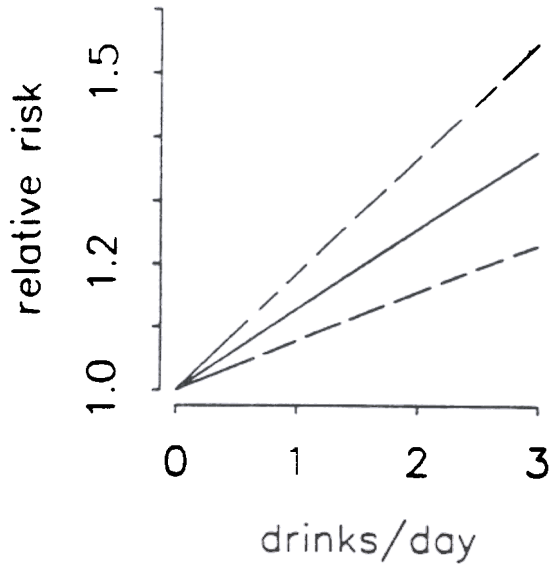

Figure 1. Dose–response curve reflecting the association between alcohol consumption and breast cancer risk in data from 38 observational epidemiologic studies. Broken lines indicating the 95% confidence limits are shown above and below the relative risk curve (solid line).

relation of alcohol consumption and breast cancer. The most recent metaanalysis incorporated qualitative and quantitative aspects of studies. Mathematical models were fit to the pooled data, with larger studies being given greater weight than smaller ones in the estimation of the overall alcohol effect. An earlier report of this metaanalysis comprised 12 case–control and 4 cohort studies.[63] The pooling now includes 28 case–control and 10 cohort studies.[64] Updated results from this metaanalysis are shown in Figure 1.

These data clearly indicate a dose–response association between alcohol consumption and risk of breast cancer and that on average the association is modest. For example, the risk of breast cancer at a daily intake of 26 g of ethanol relative to nondrinking was 1.24 (95% confidence interval, 1.15–1.34). Results for case–control and cohort studies were not different.

Other findings of note from the metaanalysis were that there was marked variation in results from study to study, that studies from countries with the highest per capital alcohol intake tended to find stronger associations, and that follow-up studies with longer durations of follow-up tended to have weaker alcohol–breast cancer associations. The latter two factors, however, accounted for only a small portion of the variation among studies. Thus an explanation for the marked among-study variation in results is still needed.

One of the largest studies of alcohol and breast cancer was the Cancer and Steroid Hormone case–control study. In those data, as initially analyzed, there was essentially no relation between alcohol and breast can-

cer[28] (the null result was included in the metaanalysis). A more recent analysis of the same data,[58] however, showed strong evidence of a modest alcohol–breast cancer association. An explanation is needed for this within-study variation in results among analyses of the Cancer and Steroid Hormone data. Another large study that showed no association between alcohol and breast cancer was that of Harris and Wynder.[19] This was a hospital-based case–control study, and the extent to which the control subjects represented exposure in the population that gave rise to the cases is unknown. Although the analysis of data from the well-known Framingham Heart Study[30] showed no or even a slightly protective association between alcohol and breast cancer, the results should be considered in light of this being a rather small study.

It is questioned whether the alcohol association might be confined to a particular type of alcoholic beverage. Each of the broad categories of alcoholic beverages—beer, wine, and spirits—has been implicated in several studies.[6,9,10,12,16,20,28,29,31,33,42–47] If, however, one considers only positive studies in which comparisons among beverages were made after adjusting accounting for dose and intake of other beverages,[10,44] the results suggest that risk increases with consumption of alcohol in general, regardless of beverage type.

Effect Modification

Several groups of investigators have examined whether the alcohol–breast cancer association differs among women stratified by such factors as age, menopausal status, body size, exogenous estrogen usage, and family history. This is known in the epidemiologic literature as effect modification and may reflect important biologic interactions between alcohol intake and, for example, obesity or genetic susceptibility. Reports of effect modification must be interpreted cautiously, however, given the tendency for authors to report only positive effect modification findings (i.e., publication bias).[65]

Age

There are at least two pertinent questions here. First, is the association between alcohol and breast cancer greater for breast cancer diagnosed in younger women? Two early studies[10,11] found the association to be greater in younger women, but subsequent investigations[31,33,42,46,47] have not confirmed this.

Second, is consumption at an early age (as opposed to recent/current intake) associated with risk? At least four studies have suggested that breast cancer risk is elevated by drinking only in early life.[9,12,26,27] Other studies[21,43] have observed no special effect of early drinking.

One could speculate that an effect of drinking in earlier life reflects a biologic window of vulnerability. Whether breast cancer risk is particularly related to early life alcohol intake, though, remains unknown.

Menopausal Status

Studies of the effect of menopausal status on the alcohol–breast cancer association have yielded mixed results. A few studies have shown the association between alcohol and breast cancer to be greater among premenopausal as opposed to postmenopausal women,[11,26,44,52] some have shown the relation to be stronger among postmenopausal women,[9,47] and others have found the association unmodified by menopausal status.[42,46] In general, these studies have been hampered by the availability of a small number of premenopausal cases. Moreover, it is difficult to separate the effect of menopausal status from that of age.

Body Size

At least seven studies have examined the influence of body size on the alcohol–breast cancer relation.[10,11,19,38,42,46,53] Two of these[10,11] indicate a stronger association among leaner as opposed to more obese women, whereas the other studies do not demonstrate this clearly. Whether the modification of the alcohol–breast cancer relation by body size (should it turn out to be true) represents some biologic interaction of alcohol with obesity (perhaps the greater volume of peripheral adipocyte androstenedione-estrogen conversion) or some other obesity-associated factor is unclear.

Exogenous Estrogen Usage

A few recent reports have suggested that the alcohol–breast cancer association is stronger among those women who have taken[53] or are currently taking[66] replacement estrogens. Other studies[12,14,29,67] found no effect modification by estrogen usage. This warrants further investigation.

Family History

One recent study[53] has shown that the alcohol–breast cancer relation was restricted to those women with a positive family history of breast cancer; this was not reported in earlier investigations.[10,11] Whether modification of the alcohol–breast cancer link by family history reflects genetic susceptibility or some other shared exposures among affected family members is unclear.

General Methodologic Issues

Error in Alcohol Assessment

Two types of instruments have been used in epidemiologic studies to assess alcohol consumption: the food frequency questionnaire and the specifically tailored alcohol questionnaire. The question has been raised whether errors in recall or reporting of alcohol consumption could account for the observed association with breast cancer. There are two reasons why this is unlikely to be the case.

First, although there appears to be substantial error (underreporting) accompanying heavy drinking,[68] moderate and lesser levels of alcohol consumption do not appear to carry much error.[69–71] Among the spectrum of dietary factors analyzed in such studies, alcohol appears to be one of those most accurately reported.[69,72,73]

Second, nondifferential error in exposure assessment generally[74] (though not always[75]) attenuates observed relative risks. The finding that epidemiologic studies in toto demonstrate a positive (direct) alcohol–breast cancer association suggests that even if some attenuation were occurring, there is still an underlying association. Although the preceding statement is generally true, there are specific instances in which error in drinking assessment may have other consequences. For example, assume that a dose–response relation between alcohol and breast cancer exists. If heavy drinkers, regardless of whether they have developed (or are destined to develop) breast cancer, underreport their consumption but still admit to drinking, women included in the middle drinking categories (now including the underreporting and higher risk heavy drinkers) would have inflated relative risks. In a continuous analysis, the slope of the relation would be artifactually increased. Conversely, if heavy drinkers were to describe themselves as nondrinkers, then, in accordance with the general measurement error rule cited above, both the categorical and continuous results would be attenuated. It is not known, though, whether heavy drinkers are more likely to falsely report themselves as nondrinkers or lighter drinkers. Therefore, the exact effect of measurement error is difficult to determine.

Small Relative Risks

According to the metaanalysis discussed above, the relative risk for two drinks per day (compared to nondrinking) in relation to breast cancer is probably in the range of 1.2–1.3. The magnitude of association here is much less that that between cigarette smoking and lung cancer (reflected in relative risks of 10 or more in many studies).

The concern has been raised that small relative risks (i.e., 1.5 or less) are inherently unreliable in epidemiologic research and that associations of this magnitude should be considered cautiously, because bias could account for the small excess risk. It is also possible that the same type of bias would be operating across many different studies, so the consistency of the small excess risk is not per se an argument against the existence of such a bias.

The fact remains, however, that small relative risks may be the nature of biologic-epidemiologic reality for many exposures and diseases. How often are we likely to run into situations, like smoking and lung cancer or vinyl chloride and liver cancer, where the relative risks are comparatively enormous? It is plausible that many exposures could increase cancer risk by only 30% or even less. Yet, such a "small" increase in risk could have public health significance, especially when we are dealing with common exposures. Therefore, researchers must refine the tools of epidemiology and other disciplines to detect these small increases in risk. The possibility of excess risk-explaining bias does not in itself preclude the existence of such excess risks.

Confounding

Women who drink alcohol may differ from those who do not. If alcohol were not causally related to breast cancer, but drinkers had a greater prevalence of some characteristic, X, that is a causal factor, then X would be a confounder of the observed alcohol–breast cancer association. In this case, confounding bias would make it appear that alcohol is the culprit when really it is X. If, however, X could be measured reasonably well and then adjusted for in the analysis, the previously observed direct alcohol–breast cancer association would be dismissed.

It may be difficult to conceive of any lung cancer–producing factor that is 10–20 times more common in smokers than in nonsmokers. When, however, relative risks are a considerably more modest 1.2–1.3, as in the alcohol–breast cancer studies, then it is more plausible that some confounding factor could be at least as strongly associated with breast carcinogenesis as well as being associated with alcohol consumption. Most of the epidemiologic studies that have reported a direct alcohol–breast cancer link, however, have controlled for known breast cancer risk factors and other variables, and the alcohol–breast cancer finding has held up. In other words, although we cannot rule out the possibility that some breast carcinogen strongly associated with alcohol consumption may emerge, no such confounder has been identified; if one is identified, then that in itself would represent a major advance in our understanding of this disease.

Consistency of the Evidence

Virtually all competently designed epidemiologic studies of smoking and lung cancer demonstrate a strong association. This is clearly not the case for alcohol and breast cancer. There are a number of cohort and case–control studies (albeit, a minority of each type of study) that have found no direct alcohol–breast cancer association. In one sense, then, the causal criterion of consistency[74] is not met. One must consider, however, that the epidemiologic investigations taken in toto (as reflected in the metaanalysis) suggest that something is going on. It is perhaps to be expected that not all studies of a real but relatively weak association would yield positive results.

It is noteworthy that the studies underlying the metaanalysis involve considerable geographic and demographic diversity. Recent reports of a direct association between alcohol intake and breast cancer have come from still other countries, including Russia[54,55] and Spain.[56]

In addition to epidemiologic case–control and cohort studies, there have been a few studies examining breast cancer mortality among alcoholics. These studies have a number of methodologic limitations, including use of mortality rather than incidence end points, absence of confounding information, and a small number of cases. Adelstein and White, for example, identified 475 alcoholic women in the United Kingdom and found a breast cancer mortality rate approximately double what was expected.[76] Results from other such studies,[77–79] often based on a very small number of breast cancer deaths, were inconsistent.

It is often asked whether women in countries with relatively high alcohol consumption experience greater breast cancer than those in relatively light-drinking nations. This is an ecologic (or aggregate data) type of question. In one study,[80] national breast cancer rates were correlated with alcohol consumption data in an international correlation ($r = 0.3–0.6$). This result, however, was difficult to interpret because the association disappeared after control for per capita fat consumption; moreover, the national alcohol consumption figures were for men and women combined, and it cannot be assumed that the variation in total consumption is the same as that for women alone. In another type of ecologic study, Smith found that breast cancer hospital admission rates were directly correlated with alcohol consumption over a 14-year period in Australia; however, this finding held only for women age 30–59 years and not for those age 60 years and older.[81]

It is worth noting that countries with the highest per capita alcohol consumption are those with the largest alcohol–breast cancer association in case–control and follow-up studies. This is expected, because in countries with low per capita alcohol consumption, few women fall into the heavier drinking categories, which makes it difficult to make a meaningful comparison of breast cancer risk across the full range of alcohol intake.

Biologic Plausibility of the Alcohol–Breast Cancer Hypothesis

General Considerations

Demonstration of a pathophysiologic basis for the alcohol–breast cancer association would lend substantially greater credence to a hypothesis that thus far has been largely the province of observational epidemiologic studies.

A number of epidemiologic studies suggest that alcohol consumption enhances the development of aerodigestive tract cancer.[82,83] Although alcohol has been shown to operate synergistically with tobacco smoke in the genesis of these tumors, after adjustment for smoking, alcohol appears to be an independent risk factor for esophageal cancer.[82,83]

The connection between alcohol and epithelial cancers of the upper aerodigestive tract could be traced to direct contact between ethanol and target cells. For breast cancer, however, we need to invoke a biologic process by which internally absorbed ethanol influences cellular events in distant epithelial tissue.

Several pathophysiologic processes (mechanisms) by which alcohol might enhance breast carcinogenesis have been suggested, although each of these must be considered speculative.[84] Alcohol consumption might influence the following:

1. Levels of estradiol or other reproductive steroid hormones that have a putative relation with breast carcinogenesis[85,86]
2. Hepatic metabolism of carcinogens or procarcinogens[87]
3. Cell membrane integrity, thereby influencing cell-to-cell communication, which might be involved in carcinogenesis[88]
4. Production of of cytotoxic protein products[89]
5. Immunologic surveillance[84]
6. DNA repair[84]
7. Metabolism of congeners.[84]

Although these intermediate pathophysiologic processes are conjectural, the existence of plausible explanatory mechanisms—particularly the alcohol-estrogen link—lends further credence to the alcohol–breast cancer hypothesis.

Table 1. Effect of Alcohol on Serum Estradiol Concentration (pg/ml): Results of Experiments Among Premenopausal Women

Study	Author	Dose (no. of alcoholic drinks*)	Result†	Change (pg/ml) due to alcohol‡		
				Follicular	*Periovulatory*	*Luteal*
Short term studies						
Alcohol given after stimulation of anterior pituitary	Mendelson[90]	4, at once	↑ E_2	5 → 35		25 → 70
	Mendelson[91]	4, at once	↑ E_2			65 → 110
	Teoh[92]	4, at once	↑ E_2	80 → 130		
Alcohol given without prior stimulation of anterior pituitary	Mendelson[93]	4, at once	↑ E_2	10 → 35		
	Mendelson[94]	4, at once	no Δ	120 → 130		
	Valimaki[95]	4, at once	↑ E_2			165 → 205
	Becker[96]	4, at once	no Δ			165 → 140
Long term studies	Reichman[85]	2/day for 3 mo	↑ E_2		65 → 85	

E_2: serum estradiol; Δ: change; ↑: increased.

* Doses are approximate; Becker used an intravenous infusion.

† Increase or decrease noted only when statistically significant.

‡ Several values have been estimated from graphs presented in the original papers. Values at 30 minutes after alcohol dose are shown for the short term studies.

Possible Hormonal Mediation

Because of the recent and increasing interest in the possible hormonal mediation of the alcohol–breast cancer link, we discuss this particular potential mechanism in some detail. The results of short-term experiments in nonalcoholic premenopausal women (Table 1) suggest that when alcohol is given after stimulation of the anterior pituitary it increases serum estradiol. In the normal menstrual cycle, gonadotropin levels peak near the time of ovulation. In the long term experiment by Reichman et al.,[85] alcohol increased plasma estradiol levels during the periovulatory phase of the menstrual cycle—when gonadotropin levels are highest. The results of other short term experiments with alcohol given without prior stimulation of gonadotropins show mixed results. These experimental results suggest that alcohol may increase serum estradiol levels in premenopausal women, but only when gonadotropin levels are high.

In cross-sectional studies among postmenopausal women,[97] women who drank alcohol had higher estradiol levels than nondrinkers in three of the four cities where studies were done (Table 2). In postmenopausal women, gonadotropin levels are elevated and some ovarian function may remain.[99] Although confirmatory experimental evidence in premenopausal and postmenopausal women is needed, the possibility exists that alcohol augments gonadotropin-induced increases in serum estradiol levels.[86]

The Low Dose Issue

Some have wondered whether low dose alcohol intake—as little as a drink per day—could really affect breast carcinogenesis. Three arguments can be made in defense of the plausibility of such a low dose effect:

1. For virtually all known initiators, there is no lower threshold, that is, even very low doses of initiators increase cancer risk. (This is not to say that alcohol necessarily works at an initiating or early stage of carcinogenesis. It does suggest, though, that low dose exposures can play a substantial role in the carcinogenic process.)
2. As little as one drink a day has been shown to raise high-density lipoprotein cholesterol levels,[100] suggesting that other biologic effects at this level of intake are plausible.
3. Low average intake may mask binges and associated toxic levels of alcohol consumption. A woman who drinks seven drinks on each of two weekend

Table 2. Levels of Serum Estradiol in Women Who Do and Do Not Drink: Cross-sectional Data From Postmenopausal Women*

Location	Average no. of alcoholic drinks in drinkers	Result†	Mean E_2 (pg/ml) drinker	
			No	*Yes*
Pittsburgh‡	1/day	↑ E_2	28	44
Cophenhagen	1/day	↑ E_2	35	68
Lisbon	2/day	↑ E_2	42	89
Madrid	1/day	no Δ	47	45

E_2: serum estradiol; ↑: increased.

* All data were presented in the same report.[97]

† Increase or decrease noted only when statistically significant.

‡ Another report based on the same subjects in Pittsburgh showed no relation of alcohol with estradiol.[98]

Table 3. Summary of Evidence From Animal Models of Mammary Carcinogenesis in Which Alcohol was Evaluated as an Augmenting Agent

Author	Animal	Carcinogen	Alcohol		Effect of alcohol on tumor incidence	Notes
			Dose	*Route*		
		—			None	Beer given in place of water
		DMBA or MNU			None	Increased no. of tumors/rat with DMBA
Singletary[103]	Rats	DMBA	10–30% energy	Liquid diet	Increased	—
Rogers[104]	Rats	DMBA	20–25% energy	Liquid diet	None	—
McDermott[105]	Rats	DMBA	4.4 g/kg/day	Water	Decreased	Rx group weighed less
Hackney[106]	Mice*	—	4–20 g/kg/day	Water	Decreased or none	2/3 Rx groups weighed less

DMBA: dimethylbenzanthracine; MNU: methylnitrourea.
* These animals develop mammary cancer spontaneously.

days consumes an average of two drinks per day but could have an exposure experience biologically distinct from that of a woman consuming two drinks each day.

Animal Studies

Six alcohol–mammary carcinogenesis studies in rodents have been conducted (Table 3). Animals receiving alcohol experienced an increased incidence of tumors in one[103] of the six studies. Although the studies by Singletary et al.[103] and Rogers and Conner[104] were similar, Rogers and Conner found no effect of alcohol. In the Rogers and Conner study, the incidence of tumors among animals not receiving alcohol was very high, thus an effect of alcohol, if present, might have been difficult to demonstrate. In two of the other experiments in which an alcohol effect was not demonstrated,[105,106] the alcohol-treated animals weighed less than the control animals. Because body weight is a determinant of tumor incidence in animals, the results of these two studies are not strong evidence against an alcohol effect. Although the results from animal studies have been inconsistent, it is noteworthy that alcohol augments mammary carcinogenesis in one model, and this supports the biologic plausibility that alcohol might cause breast cancer in women. Nonetheless, replication of Singletary's results in other laboratories would be reassuring.

In contrast to the epidemiologic effort invested in the alcohol–breast cancer problem, it appears that animal research in this area is in its infancy.

Alcohol and Mammographic Densities

Studies of benign breast disease in relation to alcohol consumption have given mixed results. Funkhouser et al.[107] found that the odds ratio of widespread prominence of ductal tissue or dysplasia on mammography in women consuming more than three drinks per week was 1.9 (95% confidence interval, 0.8–4.5) compared with nondrinkers. Boyd et al.,[108] in data from a small study of risk factors for mammographic dysplasia, found that the average alcohol consumption among women with dysplasia was 18 g/day, compared with 5 g/day in women without dysplasia ($P = 0.01$). Rohan and Cook,[109] however, found in a large population-based study that the occurrence of biopsy-proven benign proliferative epithelial disorder of the breast was unrelated to alcohol use.

Future Research

Given the modest relative risk involved in this issue, the possibility of residual confounding, and the impossibility of performing a clinical trial of this question, more studies among diverse populations are needed. Large prospective cohort studies are especially desirable; well-designed case–control investigations may be informative, but further efforts to test for recall bias are essential.[110,111]

Several nuances of the alcohol–breast cancer relation should be targeted in future epidemiologic studies.

Temporal aspects of exposure. These aspects include early versus current drinking, drinking at specific reproductive milestones (e.g., puberty and adolescence) or during particular phases of the menstrual cycle, and cumulative alcohol consumption (few studies have attempted to ascertain this).

Quantitative aspects of exposure. Further work is needed to find the dose that increases risk. This involves capturing not only average and cumulative intake but also binge drinking.

Qualitative aspects of exposure. Studies suggest that it is ethanol per se that increases risk, but further efforts should be made to rule out effects from specific types of alcoholic beverages.

Interactions (effect modification). Research on

possible interactions of alcohol with other exposures and personal traits has been sparse and somewhat inconsistent. Future studies need to be large enough to have sufficient cases for examining these potentially important interactions. Pooling data across studies would also facilitate the detection of effect modifiers.

Combinations of the above factors. Factors such as whether binge drinking at certain ages (or key reproductive milestones) enhance breast cancer risk must be considered.

Calibration studies. Studies of the accuracy of self-reported alcohol consumption have shown that alcohol is measured reasonably well compared with other dietary factors, but further research is need on whether, for example, early drinking and bingeing can be adequately assessed in later years.[112]

Further development of animal research on the alcohol–breast cancer question is needed. A clear-cut demonstration of a biologic enhancement of animal mammary tumors by ethanol would greatly strengthen the case for the alcohol–breast cancer connection.

More metabolic studies in women of the effects of alcohol on hormones and possibly other breast cancer–related parameters (e.g., cell proliferation in ductal epithelium) are warranted. At a minimum, the kind of study done by Reichman et al.[85] should be confirmed in other premenopausal women and in postmenopausal women as well.

Conclusion

A causal relation between alcohol consumption and breast cancer has not been proven. However, the weight of epidemiologic and other types of evidence suggests that something is going on. The possibility of finding a modifiable cause of breast cancer—whether it is alcoholic beverages per se or something closely associated with alcohol consumption—is one that cannot be ignored.

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